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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Therapeutic Preparation for Inhalation

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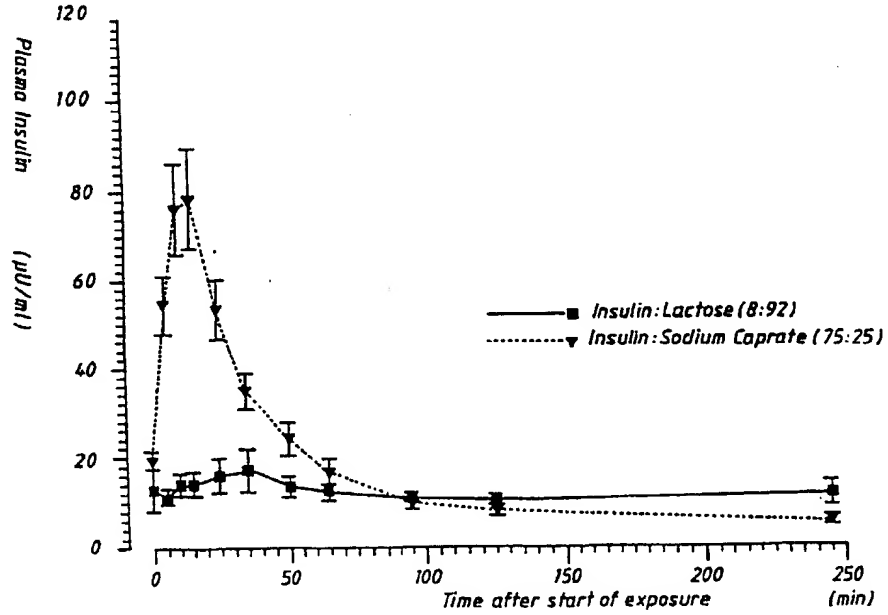

(57) Abstract

A therapeutic preparation for inhalation which comprises insulin and a substance which enhances the absorption of insulin in the lower respiratory tract, is provided in the form of a powder preparation suitable for inhalation.

Claims

1. A therapeutic preparation, comprising active compounds (A) insulin and (B) a substance which enhances the absorption of insulin in the lower respiratory tract, in the form of a dry powder suitable for inhalation in which at least 50% of the total mass of active compounds consists of (a) particles having a diameter of up to 10 microns or (b) agglomerates of such particles.

2. A therapeutic preparation as claimed in claim 1, characterised in that the therapeutic preparation contains only said active compounds.

3. A therapeutic preparation as claimed in claim 1, characterised in that the dry powder contains, in addition to said active compounds, a pharmaceutically acceptable carrier.

4. A therapeutic preparation as claimed in claim 3, characterised in that said carrier consists of particles having a diameter of up to 10 microns such that at least 50 % of said dry powder consists of (a) particles having a diameter of up to 10 microns or (b) agglomerates of such particles.

5. A therapeutic preparation as claimed in claim 3, characterised in that said carrier consists of coarse particles, such that an ordered mixture may be formed between said active compounds and the carrier.

6. A therapeutic preparation as claimed in claim 4, in which at least 50 % of the dry powder consists of (a) particles having a diameter of between 1 and 6 microns or (b) agglomerates of such particles.

7. A therapeutic preparation as claimed in claim 1 or claim 5, in which at least 50 % of the total mass of active compounds (A) and (B) consists of particles

having a diameter of between 1 and 6 microns.

8. A therapeutic preparation as claimed in claim 1, characterised in that the insulin is bovine, porcine, biosynthetic or semisynthetic human insulin, or a biologically active derivative of human insulin.

9. A therapeutic preparation as claimed in claim 8, characterised in that the insulin is semisynthetic human insulin.

10. A therapeutic preparation as claimed in claim 8, characterised in that the insulin is a biosynthetic human insulin.

11. A therapeutic preparation of insulin as claimed in claim 1, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is a substance which promotes the absorption of insulin through the layer of epithelial cells in the lower respiratory tract and into the adjacent pulmonary vasculature.

12. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is a surfactant.

13. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is an anionic surfactant.

14. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is a bile salt or a bile salt derivative.

15. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is a phospholipid.

16. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is an alkyl glycoside.

17. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is a cyclodextrin or derivative thereof.

18. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is the salt of a fatty acid.

19. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is a salt of capric acid.

20. A therapeutic preparation as claimed in claim 11, characterised in that the substance which enhances the absorption of insulin in the lower respiratory tract is sodium caprate.

21. A therapeutic preparation comprising active compounds (A) insulin and (B) sodium caprate, which preparation is in the form of a dry powder suitable for inhalation, in which at least 50 % of the total mass of active compounds (A) and (B) consists of (a) primary particles having a diameter of less than 10 microns, or (b) agglomerates of such particles.

22. A therapeutic preparation as claimed in claim 21, containing only said active compounds.

23. A therapeutic preparation as claimed in claim 21, characterised in that the dry powder contains, in addition to said active compounds, a pharmaceutically acceptable carrier.

24. A therapeutic preparation comprising insulin, sodium caprate and a pharmaceutically acceptable carrier, which preparation is in the form of a dry powder suitable for inhalation of which at least 50% by mass consists of (a) particles having a diameter of less than about 10 microns, or (b) agglomerates of said particles.

25. A therapeutic preparation, comprising

active compounds (A) insulin and (B) sodium caprate wherein at least 50 % of the total mass of active compounds (A) and (B) consists of particles having a diameter of less than about 10 microns, and

a pharmaceutically acceptable carrier,

which preparation is in the form of a dry powder preparation suitable for inhalation in which an ordered mixture may be formed between the active compounds and the pharmaceutically acceptable carrier.

26. A therapeutic preparation as claimed in claim 1 or claim 21, characterised in that the ratio of insulin to enhancer in said preparation is in the range 9:1 to 1:1.

27. A therapeutic preparation as claimed in claim 1 or claim 21, characterised in that the said ratio is in the range 5:1 to 2:1.

28. A therapeutic preparation as claimed in claim 1 or claim 21, characterised in that the said ratio is in the range 4:1 to 3:1.

29. A therapeutic preparation as claimed in claim 3 or claim 23, characterised in that the additive is selected from mono-, di-, and polysaccharides, sugar alcohols and other polyols.

30. A therapeutic preparation as claimed in claim 3 or claim 23, characterised in that the additive is a non-reducing sugar.

31. A therapeutic preparation as claimed in claim 30, characterised in that the additive is raffinose, melezitoze, lactitol, maltitol, trehalose, sucrose, mannitol or starch.

32. Use of a therapeutic preparation as claimed in claim 1 or claim 21, in an inhalation device.

33. Use as claimed in in claim 32, characterised in that the inhalation device provides protection of the powder for inhalation from moisture, and has minimal risk of overdosing.

34. Use as claimed in claim 32, characterised in that the inhalation device is a single dose, breath actuated, dry powder inhaler for single usage.

35. Use as claimed in claim 32, characterised in that the inhalation device is a multi dose, breath actuated, dry powder inhaler for multiple use.

36. A dry powder inhaler device containing the therapeutic preparation of claim 1 or claim 21.

37. A single dose, breath actuated, dry powder inhaler for single usage, containing a therapeutic preparation for inhalation, which preparation comprises active compounds (A) insulin and (B) sodium caprate and is in the form of a dry powder in

which at least 50% of the total mass of active compounds (A) and (B) consists of particles having a diameter of up to 10 microns.

38. A process for the manufacture of a therapeutic preparation of insulin, comprising forming a solution of insulin and a substance which enhances the absorption of insulin in the lower respiratory tract, removing the solvent by evaporation or otherwise to obtain a solid, and optionally grinding and/or mixing said solid to obtain a powder of which at least 50% consists of particles which have a diameter of up to 10 microns.

39. A process as claimed in claim 38, comprising adding, in addition to said substance which enhances the absorption in the lower respiratory tract, a pharmaceutically acceptable carrier.

40. A process for the preparation of a therapeutic preparation of insulin, comprising dry-mixing insulin together with a substance which enhances the absorption of insulin in the lower respiratory tract, and optionally grinding and/or mixing said solid to obtain a powder of which at least 50% consists of particles which have a diameter of up to 10 microns.

41. A process as claimed in claim 40, comprising dry-mixing a pharmaceutically acceptable carrier together with the insulin and substance which enhances the absorption of insulin in the lower respiratory tract.

42. A process as claimed in claim 38 or 40, comprising the additional step of micronising the preparation.

43. A process as claimed in claim 39 or 41, comprising the additonal step of preparing an ordered mixture of the said powder with a pharmaceutically acceptable carrier.

44. Use of an enhancer in the preparation of an inhalable dry powder preparation of insulin with enhanced systemic absorption of insulin in the lower respiratory tract, in which at least 50% of the total mass of insulin and enhancer consists of (1) particles having a diameter of 10 microns or less, or (2) agglomerates of said particles.

45. Use according to claim 44, wherein the enhancer is a surfactant.

46. Use according to claim 44, wherein the enhancer is a salt of a fatty acid.

47. Use according to claim 44, wherein the enhancer is sodium caprate.

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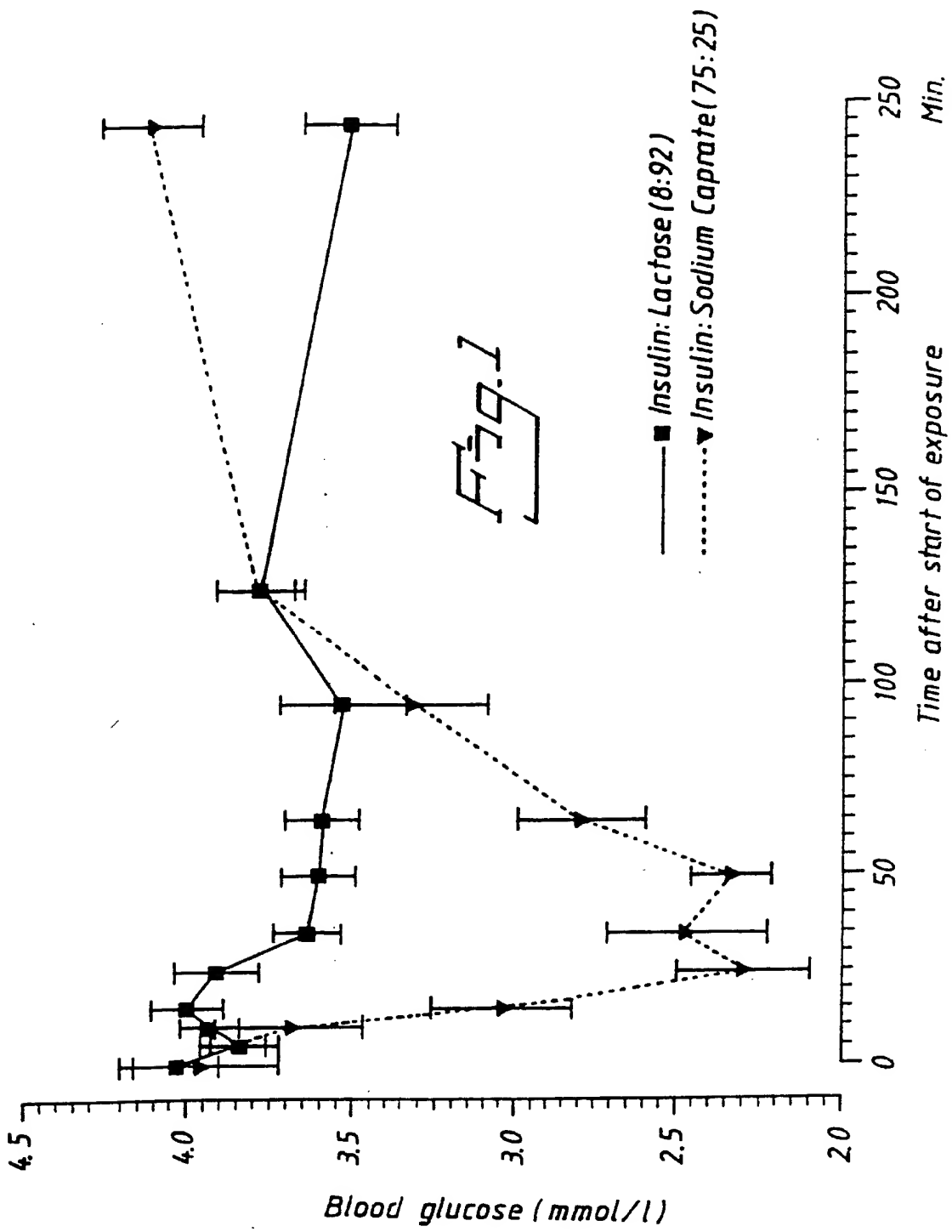
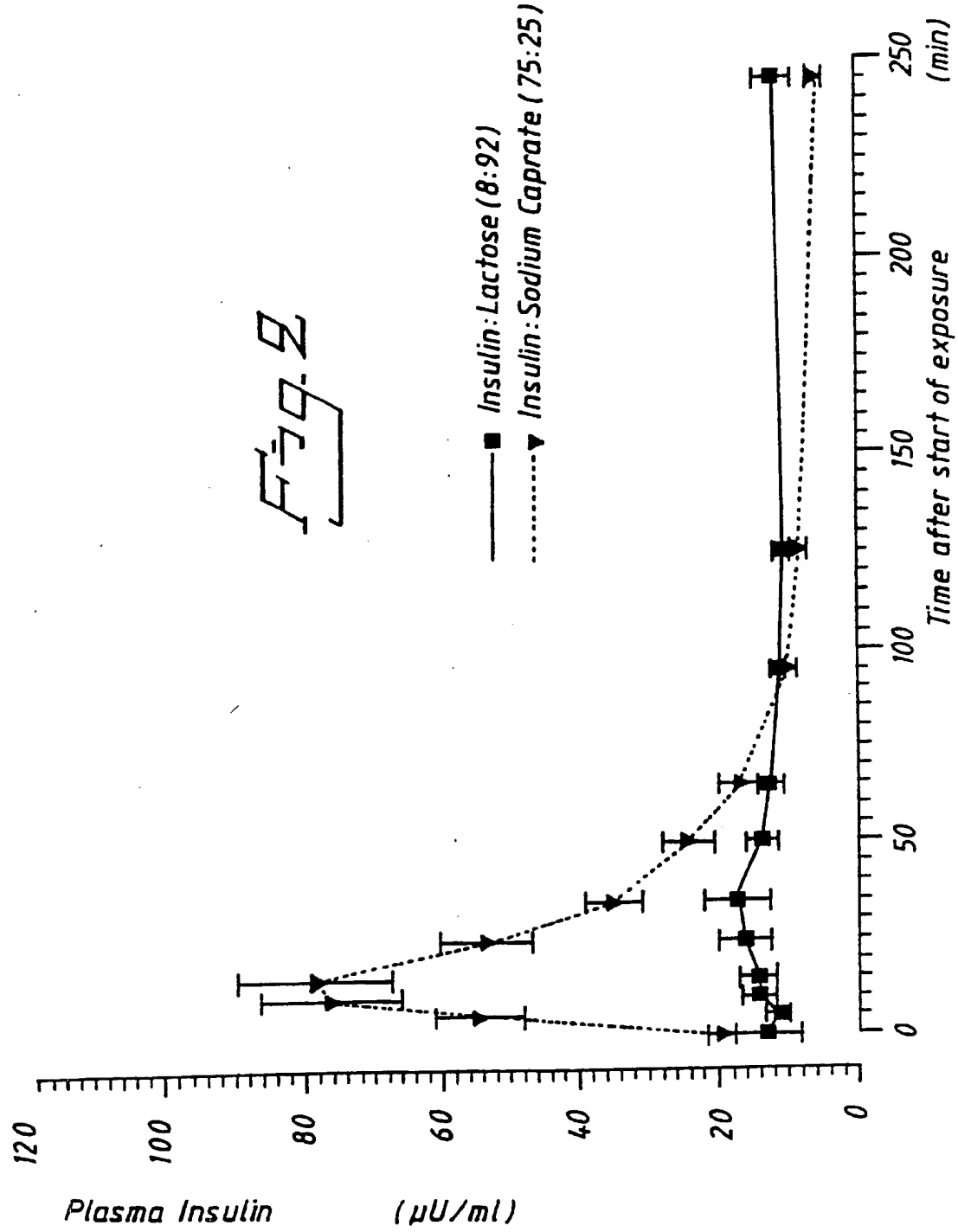


Fig. 1

Fig. 2


Insulin: Lactose (8:92)
Insulin: Sodium Caprate (75:25)
Time after start of exposure
(min)
0
50
100
150
200
250
Plasma Insulin
(μU/ml)
120
100
80
60
40
20
0

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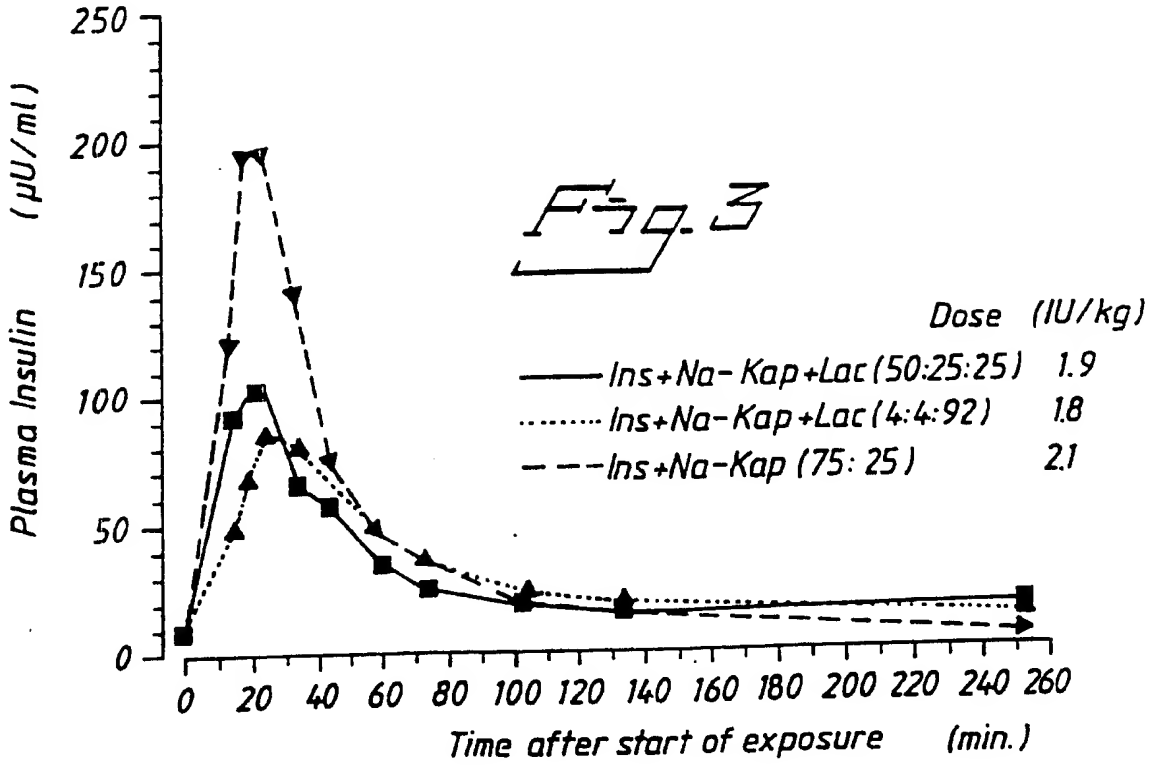

Fig. 3

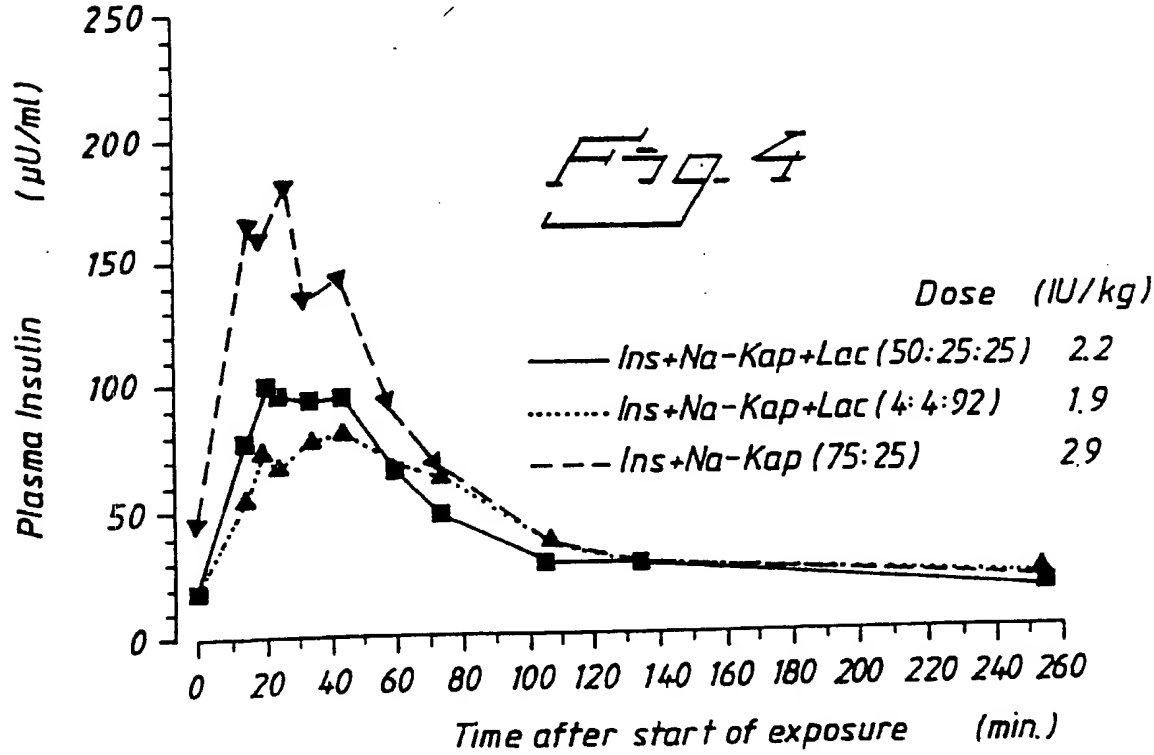

Fig. 4

Fig. 5

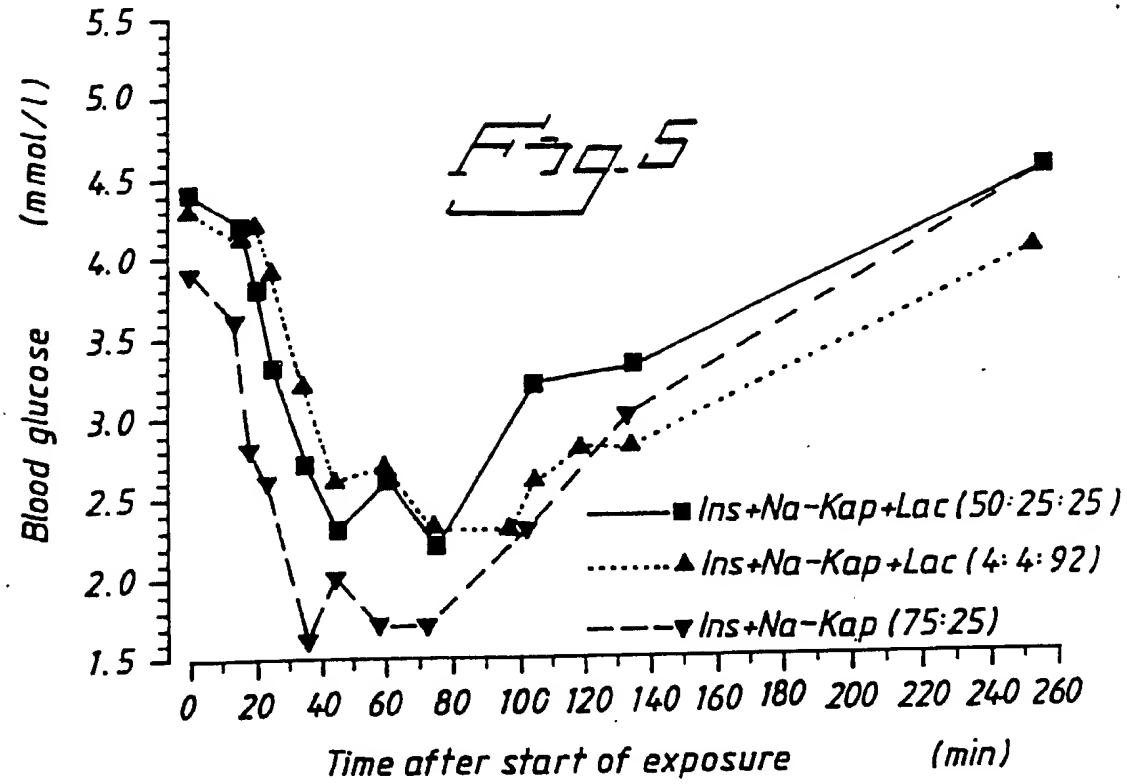
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Blood glucose (mmol/l)
0 20 40 60 80 100 120 140 160 180 200 220 240 260
Time after start of exposure (min)
Ins+Na-Kap+Lac (50:25:25)
Ins+Na-Kap+Lac (4:4:92)
Ins+Na-Kap (75:25)

Fig. 6

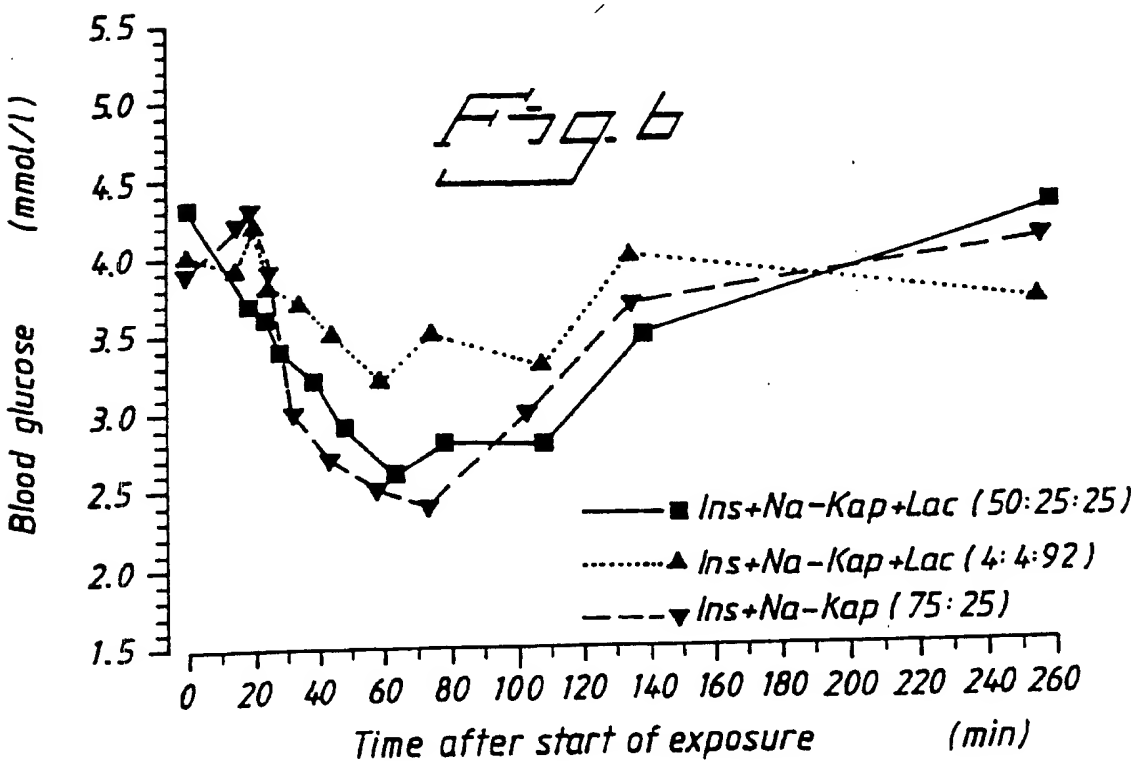
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Blood glucose (mmol/l)
0 20 40 60 80 100 120 140 160 180 200 220 240 260
Time after start of exposure (min)
Ins+Na-Kap+Lac (50:25:25)
Ins+Na-Kap+Lac (4:4:92)
Ins+Na-Kap (75:25)

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Fig. 7

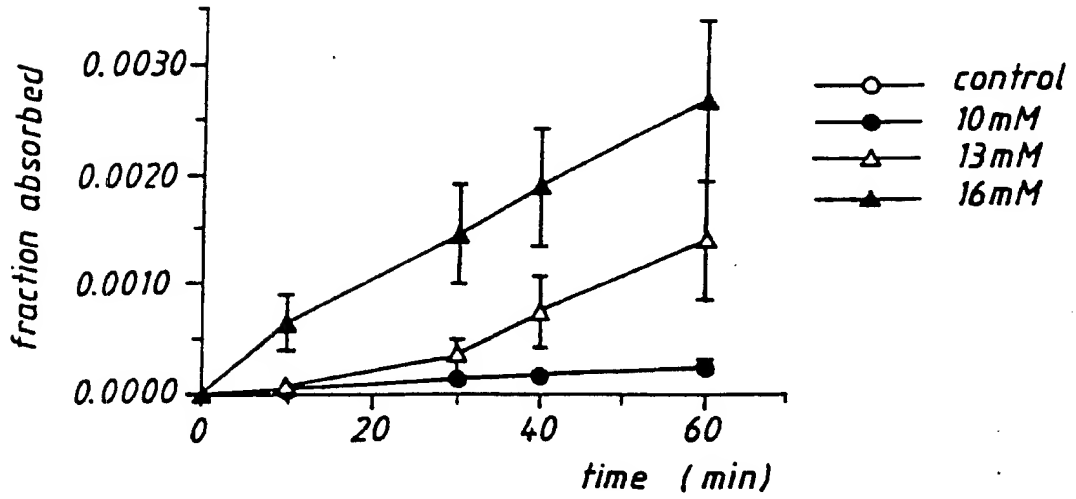


Fig. 8

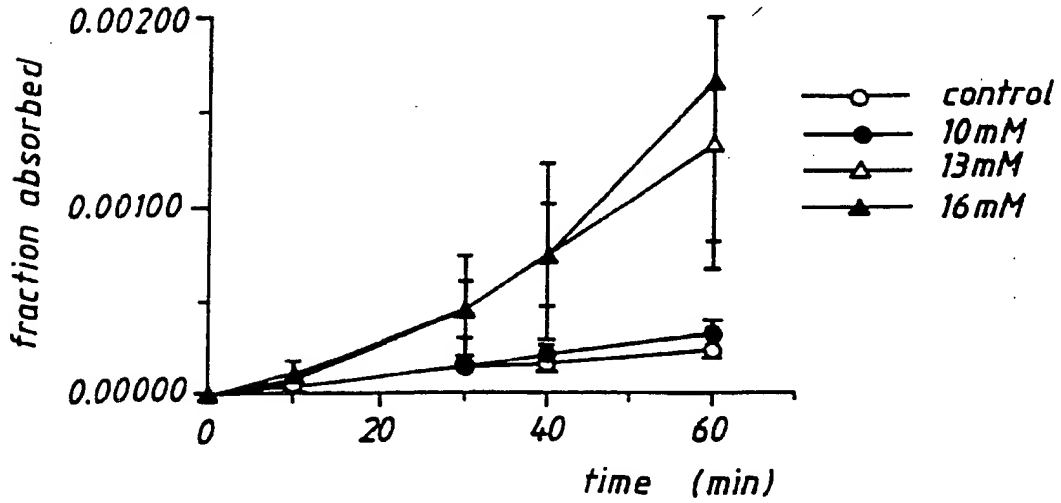
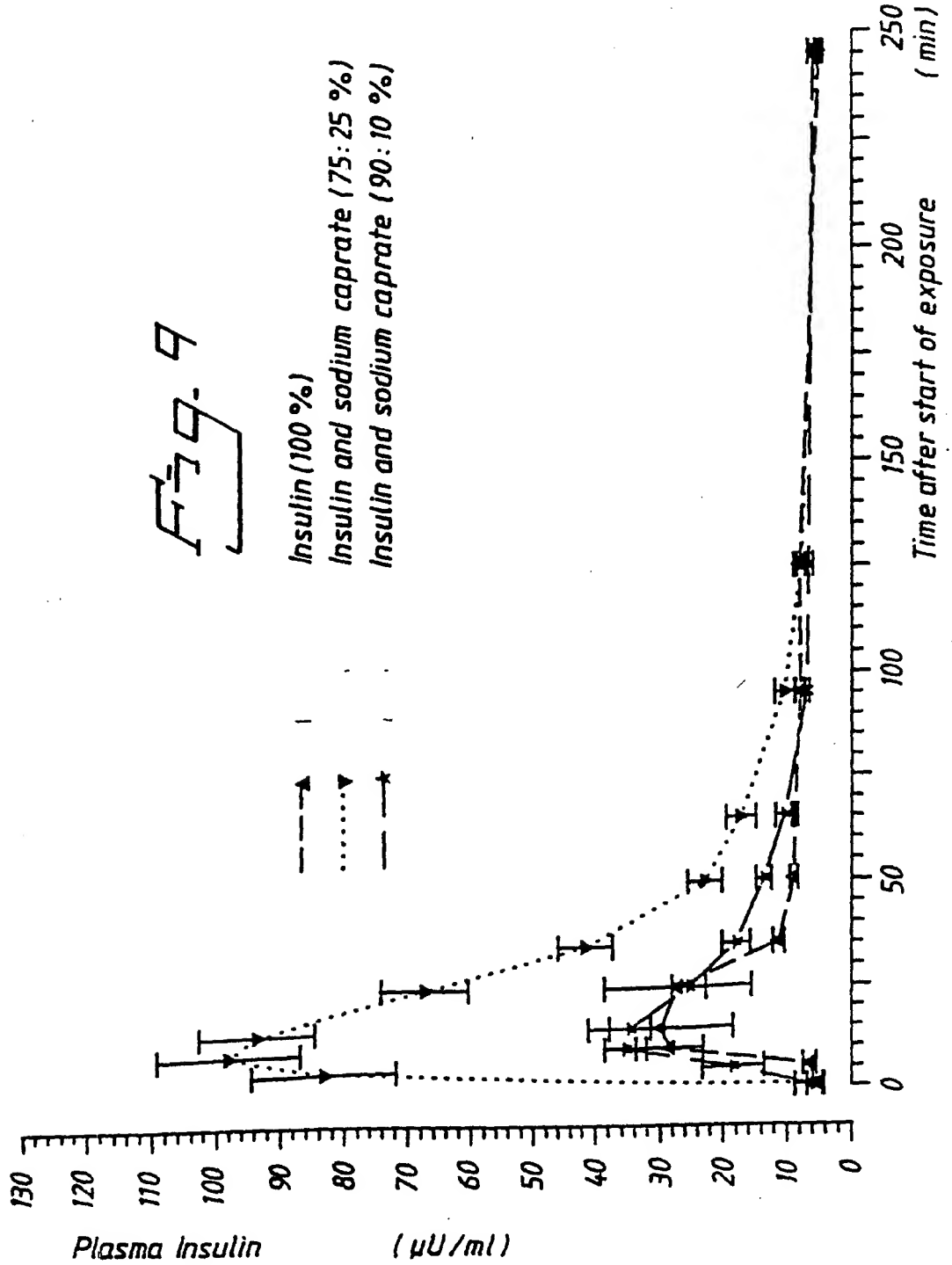


Fig. 9


Insulin (100 %)
Insulin and sodium caprate (75:25 %)
Insulin and sodium caprate (90:10 %)
Time after start of exposure (min)
0
50
100
150
200
250
Plasma Insulin (µU/ml)
0
10
20
30
40
50
60
70
80
90
100
110
120
130